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**Please find below and/or attached an Office communication concerning this application or proceeding.**

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1 RECORD OF ORAL HEARING  
2  
3 UNITED STATES PATENT AND TRADEMARK OFFICE  
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5  
6 BEFORE THE BOARD OF PATENT APPEALS  
7 AND INTERFERENCES  
8

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10 *Ex parte* ANDREW PAUL CHAPMAN and DAVID JOHN KING  
11

12  
13 Appeal 2008-0454  
14 Application 09/719,045  
15 Technology Center 1600  
16

17  
18 Oral Hearing Held: April 17, 2008  
19

20  
21 Before TONI R. SCHEINER, LORA M. GREEN, and RICHARD M.  
22 LEBOVITZ, *Administrative Patent Judges*.  
23

24 ON BEHALF OF THE APPELLANT:

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30  
31 P R O C E E D I N G S

32 MS. BEAN: Good morning.

33 JUDGE LEBOVITZ: Good morning.

34 JUDGE SCHEINER: Good morning.

35 MS. BEAN: Calendar Number 49, Mrs. Trujillo.

1 JUDGE SCHEINER: Thank you.

2 MS. BEAN: You're welcome.

3 JUDGE SCHEINER: Good morning.

4 MS. TRUJILLO: Is there any? There's nothing in there.

5 JUDGE SCHEINER: Oh, no. We can get some.

6 MS. TRUJILLO: That would be helpful, if not --

7 JUDGE SCHEINER: Of course they're not there.

8 JUDGE GREEN: They're behind you.

9 JUDGE SCHEINER: Oh. In here?

10 JUDGE LEOVITZ: It's somewhere, take a look for it.

11 MS. TRUJILLO: Sorry.

12 JUDGE SCHEINER: That's all right.

13 JUDGE LEOVITZ: Well, I see a box, but it's empty.

14 JUDGE SCHEINER: Let's see. All right, well, we can call the usher  
15 in and have some put in here.

16 MS. TRUJILLO: That's okay.

17 JUDGE SCHEINER: Other than --

18 MS. TRUJILLO: Oh, wait, they're here.

19 JUDGE SCHEINER: Oh, okay, great.

20 MS. TRUJILLO: Sorry. It was right here all along.

21 JUDGE SCHEINER: All right. Well, whenever you're ready, you'll  
22 have 20 minutes. I should point out this clock here is not working, so don't  
23 go by that.

24 MS. TRUJILLO: Okay.

25 JUDGE SCHEINER: We just noticed it this morning.

1 MS. TRUJILLO: Now, I don't think I need --

2 JUDGE SCHEINER: No, you don't have to --

3 MS. TRUJILLO: I don't think we need to worry about. Is -- so the  
4 Examiner, I don't need to reserve rebuttal. He's not attending.

5 JUDGE SCHEINER: No.

6 MS. TRUJILLO: Okay.

7 JUDGE SCHEINER: Were you told otherwise, because --

8 MS. TRUJILLO: No --

9 JUDGE SCHEINER: -- normally --

10 MS. TRUJILLO: I didn't know. I didn't know --

11 JUDGE SCHEINER: Okay --

12 MS. TRUJILLO: So, I just thought --

13 JUDGE SCHEINER: -- normally we're informed too if the  
14 Examiner has asked to attend, but --

15 MS. TRUJILLO: Okay.

16 JUDGE SCHEINER: -- we didn't hear anything, so --

17 MS. TRUJILLO: All right. May it please the Board, I'm Doreen  
18 Trujillo from Cozen O'Connor. I am representing the Applicants Chapman  
19 and King regarding Application Serial Number 09/719,045. The title of the  
20 Application is Divalent Antibody Fragments.

21 Now what Applicants are claiming in the application on appeal, as  
22 mentioned in the title, is a Divalent Antibody Fragment, but the fragment  
23 isn't just an antibody fragment, it's been modified with a polymer in a very  
24 specific way. And if you look at Claim 1 from which all the other claims  
25 depend, the claim specifies exactly where the polymer is to be attached.

1 And, if I may go over -- basically, the claim specifies that the Divalent  
2 Fragment, and divalent, basically, means of course, that there are two  
3 antigen binding domains, has at least two heavy chains with a variable  
4 region and a portion of the constant region and has two cysteine residues that  
5 are outside the variable region. Here are the variable, your constant.

6 Each chain has assisting region outside the variable domain that is  
7 involved in an interchain bridge, meaning a bridge between the two heavy  
8 chains, and that the interchain bridge is the polymer molecule. So,  
9 specifically, the claim recites that you have a divalent fragment that has its  
10 inner chain -- one of the interchain bridges not affected by a disulfide bond,  
11 but instead affected by the polymer molecule, and it's very, very specific  
12 that that's where it's to be located.

13 The example that's provided in the specification, the working example  
14 which was used to make the divalent fragment used what are called Fab'.  
15 Two Fab's were added to the polymer molecule to make the example  
16 provided.

17 JUDGE LEBOVITZ: Is Fab' the one with hinge region?

18 MS. TRUJILLO: Yes, and I'll go into that a little bit more as well.  
19 Yes, it has a little bit of the hinge, but it's not required in the claim that --

20 JUDGE LEBOVITZ: Right.

21 MS. TRUJILLO: -- it be Fab', but just that it have a Cysteine outside  
22 the variable domain in order to affect that interchain bond.

23 Now, the reason that we're so specific where the polymer is attached  
24 is because Applicants found a way to attach the polymer without sacrificing

1 antigen binding efficacy, and because in the art, some of the art, they didn't  
2 specify where it should be attached and didn't focus on antigen binding.

3 JUDGE LEBOVITZ: But, let me just ask a question: This does say a  
4 divalent antibody fragment, and you were just talking about it having, you  
5 know, conserving the binding efficacy, but it doesn't require a light chain --

6 MS. TRUJILLO: It --

7 JUDGE LEBOVITZ: -- or would that be required by divalent  
8 antibody fragments?

9 MS. TRUJILLO: There are some -- I'm sorry, there are some heavy  
10 chain-only antibodies that combine just with a heavy chain.

11 JUDGE LEBOVITZ: Okay.

12 MS. TRUJILLO: It doesn't require it, but yes, presumably it would  
13 have in many instances the light chain as well.

14 Now, just to give a little history, it's kind of like the story of  
15 Goldilocks. The reason that we got to divalent antibody fragments with  
16 polymers is because when people first started using antibodies in vivo for  
17 diagnostics or for therapy, they had -- they found that their circulating time  
18 in the body was a little too long and caused problems with background for  
19 diagnosis and also binding to healthy cells for therapy because antibody  
20 molecules are so big. They're about 150,000 molecular weight.

21 So, they were looking for an alternative because they stayed around  
22 too long, and when it came -- they developed fragments, ways to fragment  
23 the antibodies and still have antigen binding, they learned that the fragments  
24 were too small. So, the antibody, the whole antibody was too big, and the  
25 fragments were too small so they looked for something intermediate, and

1 that's where they came up with adding polymers which would give the  
2 fragments a large effective size. But, as I said, at first they weren't really  
3 focusing upon where they were attaching them. And -- leave that over here.

4 So, if you have a whole antibody -- so here's -- again, the heavy  
5 chains are the longer chains, and the light chains, they're attached. When  
6 they first did the fragments, they used enzymes to digest the antibodies. One  
7 enzyme was papain, and it digested above this heavy chain disulfide bridge.  
8 So, you ended up with two monovalent Fab fragments from the two original  
9 heavy chains and light chains. That was papain. But, when they used  
10 another enzyme, Pepsin, this would digest below the disulfide bridge so  
11 you'd end up what, with this whole thing was called an Fab' sub2. So, it  
12 would be basically contained still the bridge, and if you were to reduce that,  
13 you would end up with two Fab's.

14 JUDGE LEBOVITZ: We're pretty familiar with --

15 MS. TRUJILLO: Okay, I --

16 JUDGE LEBOVITZ: -- the -- biology.

17 MS. TRUJILLO: Yeah, just stop me --

18 JUDGE LEBOVITZ: So, we should get -- let's talk about Gonzalez  
19 then.

20 MS. TRUJILLO: Okay. So the reference is cited against the  
21 Applicants as you raised is the Gonzalez Patent. The reason I went into that  
22 is because I think it's very important --

23 JUDGE LEBOVITZ: Correct.

24 MS. TRUJILLO: -- part of the Examiner's rejection. The Gonzalez  
25 Patent was cited for both rejections. There are two rejections: an

1 anticipation or, in the alternative, obviousness rejection and over Gonzalez  
2 alone, and then an obviousness rejection over Gonzalez in view of Barbanti.

3 And, I could see the offices in the Examiner's frustration with  
4 Gonzalez because if you've seen the reference, I brought it here, it's like  
5 about one or two pounds. There are 206 columns, 136 drawings. Surely,  
6 somewhere in this reference there must be a disclosure of what Applicants  
7 are claiming, but unfortunately, there is not.

8 Gonzalez does have a lot of disclosure, does have discussion  
9 regarding polymers, does have discussion regarding Fab', Fab' sub2, but  
10 what Gonzalez doesn't have is a disclosure, again, going back to the  
11 Applicant's claim which it requires that the polymer essentially function as  
12 the interchain bridge between two cysteines outside the variable domain on  
13 the heavy chain.

14 JUDGE LEBOVITZ: But, doesn't Gonzalez tell you in Column 19  
15 that the Examiner pointed to that putting the polymers such as PEG in the  
16 hinge region, hinge region of an Fab fragment is one of -- is a preferred  
17 embodiment?

18 MS. TRUJILLO: Yes, it does, and that, and that's talking about  
19 using the monovalent, the Fab', and it talks about attaching it to the hinge,  
20 and it even has an embodiments where it's using the Fab' attached to the  
21 hinge, but then when you look at other discussion with when it's a divalent,  
22 the discussion were, the Examiner relies on the citation to the dumbbell  
23 shape where you have one polymer with two antibodies attached. There's  
24 no discussion about where, where it should be attached. It doesn't specify  
25 that you should attach it to the particular cysteine. There are various -- it



1 discloses other points of attachment, other amino acids, lysine, other -- so  
2 it's not necessarily the only place of attachment.

3 In terms of the monovalent Fab', it does mention hinge, but --

4 JUDGE SCHEINER: But, they do talk about in the preceding  
5 paragraph on Column 35 up top of putting it on a hinge region.

6 MS. TRUJILLO: I'm sorry.

7 JUDGE SCHEINER: On, on Column 35 of Gonzalez, they do talk  
8 about putting -- the PEG molecule being attached to the hinge region.

9 MS. TRUJILLO: Right, but it's monovalent. When they talk --

10 JUDGE SCHEINER: But, then they say in other embodiments -- I  
11 mean, if you're going to read those two paragraphs together, I think an  
12 ordinary artisan would get out of it that you could put this on the hinge  
13 region and get a dumbbell shape.

14 MS. TRUJILLO: Okay. Well, the problem is when you read the  
15 whole reference, again, it doesn't specifically point you to that. It's talking  
16 mainly about the monovalent, and basically it doesn't specifically disclose  
17 that. So perhaps you can say it could lead you to that, but that's not  
18 anticipation.

19 JUDGE LEBOVITZ: Well, Number 1, the Examiner does say  
20 anticipation or, alternatively, obviousness.

21 MS. TRUJILLO: Right.

22 JUDGE LEBOVITZ: At Number 2 since you draw on it, how else  
23 would you draw a dumbbell shape if it --

24 MS. TRUJILLO: Well, it could be any way. I mean, they don't  
25 really describe it, and they specifically state -- and this is the thing that

1 we've had a problem with all along. If you're not in an anticipation, then  
2 you have to consider what Gonzalez is saying about the Fab' 2. And  
3 whenever they're talking about using the cysteine, it always mentions  
4 whether it's the cysteine between heavy and light chain or the cysteine  
5 between heavy chains.

6 Gonzalez specifies that the other cysteine should be changed so that  
7 their polymer isn't working as an interchain bridge between the two chains.

8 JUDGE LEBOVITZ: Well, what the -- no, I mean, what in that  
9 example -- you know, we agree that they do say when you're in certain Fab  
10 fragments, when you're connecting the light chain to the heavy chain you  
11 would attach the polymer to a cysteine on one chain and then the other chain  
12 you would remove the cysteine there, but you'd still have a bridge so the  
13 cysteine, would still be in -- at least one cysteine would still be involved in  
14 the bridge.

15 MS. TRUJILLO: Right, but they specifically state when it's, as I  
16 said, not only between the heavy and light chain but the heavy and heavy  
17 chain for the Fab' 2 that you always make sure that the other amino acid is  
18 not a Cysteine so that it doesn't form the covalent bond as required in our  
19 claims. And that's been -- as I said, that's been our argument all along.

20 If you look at Column 21, Lines 50 to 60, in yet another embodiment  
21 the conjugate contains an Fab' sub2 wherein every polymer molecule is  
22 attached to a Cysteine residue in the light or heavy chain of the antibody  
23 fragment that would ordinarily form the disulfide bridge linking the light and  
24 heavy chains, wherein the disulfide bridge is avoided by substituting another

1 amino acid such as serine for the corresponding Cysteine residue in the  
2 opposite chain.

3 JUDGE LEBOVITZ: But, what about the Examiner's argument that  
4 -- I think on Line -- Columns 120 to 122, the example he gives you the  
5 patent describes the exact chemistry for putting a polymer on a Cysteine  
6 residue.

7 MS. TRUJILLO: But, it's a different procedure. If you read the  
8 procedure then from what we do, they recite that you have the Fab' and five  
9 molar equivalents of the polymer. When you read our procedure, we have a  
10 molar ratio of the Fab 2.2 to 1, to the polymer.

11 JUDGE LEBOVITZ: But, that's not in the claim, correct?

12 MS. TRUJILLO: Right, that's not in the claim.

13 JUDGE LEBOVITZ: Okay.

14 MS. TRUJILLO: But, if you're arguing inherency, if you're trying to  
15 say Gonzalez would get to that eventually, Gonzalez has -- even though they  
16 did that procedure, they don't -- they give the example and, and the gel, the  
17 SDS gel, there's nothing about a divalent fragment. They didn't come up  
18 with a divalent and a body bound to the polymer. So, that's basically been  
19 our argument all along. One thing that the Examiner argued was, well yeah  
20 you're not starting out with a divalent Fab' sub2, you're starting with a Fab'  
21 in your example.

22 Again, we're not limited to that. But even though we're starting out  
23 with the Fab', we're virtually ending up with the same thing that they tell  
24 you not to make because we're back to -- we're combining the Fab's with

1 the polymer as the bridge and we're ending up with exactly what Gonzalez  
2 tells you not to end up with, is an Fab' 2 with a polymer bridge.

3 JUDGE LEBOVITZ: Well, he -- but the -- Gonzalez does say if  
4 you've got a hinge region there then he tells you, you can put a Cysteine,  
5 you can put a PEG onto the Cysteine in the hinge region and then on  
6 Column 1, Line 40, it does say that PEG attached to a sulfhydryl group in  
7 the hinge region of the Fab' fragment has reduced clearance. So, based on  
8 that, based on those two things, a skilled worker reading it, wouldn't they be  
9 invariably led to putting the PEG on the hinge and also when you want to  
10 create a divalent hooking them up through the polymer on the hinge?

11 MS. TRUJILLO: That's -- our argument has been in view of this  
12 specific discussion of, of voiding the interchain bridge when you have a  
13 divalent that it might but for that, and you have to consider the whole  
14 reference. And it -- every time it talks about the interchain bridge with the  
15 cysteines between the light chain or the heavy, and heavy chain or the heavy  
16 chain and heavy chain, it specifies that the statement that I just read to you  
17 previously, is that you change the Cysteine in the other chain so that the  
18 interchain bridge is avoided.

19 And, so that's been our, our argument all along has been if you're not  
20 in -- it doesn't anticipate and it doesn't because it doesn't disclose the  
21 particular structure that we're claiming. Then, if you're looking at  
22 obviousness you have to consider the whole reference. And, the part of the  
23 reference that's discussing divalent antibody fragments, regardless of how  
24 you get there, is purposely stating that it does not want an interchain bridge.  
25 And, when you look at Gonzalez, it makes sense because their polymers are

1 gigantic. I mean, they're suggesting polymers of 100,000 molecular weight  
2 and higher because they were focusing upon just making it bigger, making it  
3 appear bigger, so they weren't even looking at antigen binding. They  
4 weren't considering antigen binding or anything else. And, so they didn't,  
5 they purposely said, keep that interchain bridge from, from forming. So,  
6 that's, that's been our argument.

7 JUDGE LEBOVITZ: Well, the interchain bridge forms -- I think the  
8 difference is it only has one sulfur in there. I mean, there is -- they've got to  
9 hook the light -- they are talking about hooking the light chain to the heavy  
10 chain. What they're, what they're talking about is a production problem, I  
11 suppose, they don't explain it that perhaps if you had both cysteines present,  
12 you might preferably get a bridge warming before attaching the PEG to it,  
13 but they actually do have inner change, inter chain bridge there.

14 JUDGE SCHEINER: Where it says in every polymer molecule is  
15 attached to a Cysteine residue that would ordinarily form the disulfide  
16 bridge. So --

17 JUDGE LEBOVITZ: The disulfide, right.

18 MS. TRUJILLO: Right.

19 JUDGE LEBOVITZ: Not, not --

20 MS. TRUJILLO: And, that's the bridge --

21 JUDGE LEBOVITZ: Not an interchain bridge.

22 MS. TRUJILLO: Well, they don't want, right, but, but that's what  
23 I'm referring to when I said the interchain bridge, it's the disulfide bridge  
24 normally that's holding the two heavy chains together for the divalent or the  
25 heavy and light chain together. And, they say wherein the disulfide bridge is

1 avoided by substituting another amino acid such as serine for the  
2 corresponding Cysteine residue in the opposite chain.

3 So, it's not even where -- as we specify, where we specify that the  
4 polymer is attached to cysteines on each heavy chain and the polymer is the  
5 interchain bridge, Gonzalez is saying, no, I don't want the polymer to be  
6 involved in an interchain bridge in a divalent antibody fragment.

7 And, then we addressed, I guess, anticipation in the genus species of  
8 course and even under KSR under an obvious to try standard, you know,  
9 there has to be a finite number and as I stated, you know, these, it could be  
10 attached anywhere. There are 110 amino acids on the, the full chains, so  
11 they don't really specify. There's not really a lot of guidance and including  
12 the teaching away of avoiding the bridge between the two chains, it, it's  
13 been our position and we maintain that Gonzalez does not anticipate and  
14 does not render obvious Applicant's snippets claims.

15 And, then regarding Barbonti, Barbonti is specifically related to the  
16 TNF alpha, the particular antigen and it describes using the whole antibody  
17 against the antigen and then it mentions that fragments can be used, but  
18 there's no mention of any problems or issues. The Examiner did raise, you  
19 know, that basically said that his standard was it would only have been a  
20 person having less than ordinary skill in the art who would've not been  
21 motivated to extend the half life of an antibody that is being administered for  
22 the purpose of neutralizing an inflammatory molecule such as TNF's alpha.  
23 Well, this really isn't the proper standard.

24 The proper standard is would a person of ordinary skill have been  
25 motivated. So, I think the Examiner kind of cites the whole burden

1 there by making conclusionary statement that only a person who wasn't of  
2 ordinary skill wouldn't have done so. And, even after KSR, this is  
3 something that, that's not allowed. So, again, Applicants maintain that their  
4 claim which specifies that the polymer is to be attached in the specific  
5 location to cysteine residues on each heavy chain is not disclosed or  
6 suggested by Gonzalez.

7 JUDGE SCHEINER: Just one more question from me. I don't know  
8 if other, but I just caught a paragraph out -- granted it's out of context. In  
9 Column 41 --

10 MS. TRUJILLO: Okay.

11 JUDGE SCHEINER: Starting at about Line 35, and as I said, it's out  
12 of context. I haven't read it with, in conjunction with the other parts, but it  
13 says that in one embodiment polymer contains only a single group which is  
14 reactive this helps to avoid cross linking of protein molecules, however, it is  
15 within the scope herein to maximize reaction conditions to reduce cross  
16 linking or to purify the reaction products through gel filtration in other --  
17 blah, blah, blah --

18 MS. TRUJILLO: Right.

19 JUDGE SCHEINER: In other embodiments, the polymer contains  
20 two or more reactive groups for the purpose of linking multiple antibody  
21 fragments to the polymer back from --

22 MS. TRUJILLO: Right again --

23 JUDGE SCHEINER: Okay, so how is that --

24 MS. TRUJILLO: -- that's similar to the dumbbell. It doesn't tell you  
25 where --

1 JUDGE SCHEINER: Where, but --

2 MS. TRUJILLO: It doesn't specify.

3 JUDGE SCHEINER: But, they are deliberately linking to -- I mean,  
4 how does this paragraph play into --

5 MS. TRUJILLO: I view it as the dumbbell paragraph. It's telling  
6 you, okay, you can attach this, but then you look at the specific disclosure  
7 saying, but we don't want it to be between two cysteines and form an  
8 interchain bridge. So, it's saying yeah, you can use this; you can use the  
9 polymer --

10 JUDGE SCHEINER: Well, how else would you envision the -- I  
11 mean, I understand that there are many cites where you can link these, but  
12 do we agree that that dumbbell implies a --

13 MS. TRUJILLO: No.

14 JUDGE SCHEINER: -- no, no, I'm no saying that implies a  
15 symmetrical structure.

16 MS. TRUJILLO: I'm not going to --

17 JUDGE SCHEINER: Bilaterally symmetrical structure.

18 MS. TRUJILLO: -- I, I, I'm sorry; I'm not going to agree because I  
19 think that that statement is just kind of thrown out there. In a typical, I  
20 mean, this, this patent is no longer even -- it's expired because they stopped  
21 paying the maintenance fees, so it's just kind of like -- I think it's a  
22 statement that's thrown out there and you're reading into it because in  
23 base -- if you didn't have our claims saying that we're have two heavy  
24 chains and it's connected by the polymer is the interchain bridge, you, you  
25 wouldn't necessarily think of it being there, and then if you -- even without



1   ours, you have the disclosure in Gonzalez stating, yeah but if you have  
2   divalent fragments we don't want the polymer to be the interchain bridge,  
3   and I -- as I said, that's been our position all along. You can't ignore that.  
4   You have to consider the whole reference. You -- I've, I've highlighted the  
5   exact statement you said, but in my view it's the same thing as the dumbbell.  
6   It's not telling you exactly where.

7           JUDGE SCHEINER: Okay. All right, I don't have anything further.  
8   Do you?

9           JUDGE LEBOVITZ: No, I'm okay.

10          MS. TRUJILLO: Thank you, very much.

11          (Whereupon, the proceedings concluded at on April 17, 2008)

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